**QUEEN'S
UNIVERSITY
BELFAST**

Serum cholesterol and risk of high-grade prostate cancer: results from the REDUCE study

Jamnagerwalla, J., Howard, L. E., Allott, E. H., Vidal, A. C., Moreira, D. M., Castro-Santamaria, R., Andriole, G. L., Freeman, M. R., & Freedland, S. J. (2018). Serum cholesterol and risk of high-grade prostate cancer: results from the REDUCE study. *Prostate Cancer and Prostatic Diseases*, 21(2), 252-259.
<https://doi.org/10.1038/s41391-017-0030-9>

Published in:
Prostate Cancer and Prostatic Diseases

Document Version:
Peer reviewed version

Queen's University Belfast - Research Portal:
[Link to publication record in Queen's University Belfast Research Portal](#)

Publisher rights
© 2018 Springer Nature Limited. All rights reserved.
This work is made available online in accordance with the publisher's policies. Please refer to any applicable terms of use of the publisher.

General rights
Copyright for the publications made accessible via the Queen's University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The Research Portal is Queen's institutional repository that provides access to Queen's research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact openaccess@qub.ac.uk.

Serum cholesterol and risk of high-grade prostate cancer: results from the REDUCE study

Juzar Jamnagerwalla, M.D.¹, Lauren E. Howard. M.S.^{2,3}, Emma H. Allott, Ph.D.^{4,5,6}, Adriana C. Vidal, Ph.D.¹, Daniel M. Moreira, M.D.⁷, Ramiro Castro-Santamaria, M.D.⁸, Gerald L. Andriole, M.D.⁹, Michael R. Freeman, Ph.D.¹, Stephen J. Freedland, M.D.^{1,3}

¹Division of Urology, Department of Surgery, Cedars-Sinai Medical Center, Los Angeles, CA, USA

²Department of Biostatistics and Bioinformatics, Duke University, Durham, NC, USA

³Surgery Section, Durham VA Medical Center, Durham, NC, USA

⁴Department of Nutrition, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

⁵Department of Histopathology and Morbid Anatomy, Trinity Translational Medicine Institute, Trinity College Dublin, Dublin, Ireland

⁶Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, MA, USA

⁷Mayo Clinic, Department of Urology, Rochester, MN, USA

⁸GlaxoSmithKline Inc., R&D, King of Prussia, PA, USA

⁹Washington University School of Medicine in St. Louis, St. Louis, MO, USA

Running title: Cholesterol and high-grade prostate cancer risk

Key words: cholesterol, low-density lipoprotein, high-density lipoprotein, prostate biopsy

Financial support: This study was supported by NIH 1K24CA160653 (S.J. Freedland), and by the American Institute for Cancer Research (E.H. Allott), and Irish Cancer Society John Fitzpatrick Fellowship (E.H. Allott)

Corresponding author: Dr. Stephen J Freedland; Mailing address: Cedars Sinai Medical Center, 8635 West 3rd Street, Suite 1070W, Los Angeles, CA 90048, USA; Tel: 310-423-3497; Fax: 310-423-4711; Email: stephen.freedland@cshs.org

Word count: 2,550 (excluding abstract and references), Abstract 264; Number of Tables: 3;

Number of Figures: 0

Abstract

Background: Epidemiologic evidence for a serum cholesterol-prostate cancer link is mixed. Prostate-specific antigen (PSA) is positively correlated with cholesterol, potentially increasing PSA-driven biopsy recommendations in men with high cholesterol, though biopsy compliance may be lower in men with comorbid conditions. These potential biases may affect PSA-driven biopsy rates and subsequent prostate cancer detection in men with high serum cholesterol. Our objective was to test the association between serum cholesterol and prostate cancer risk in men receiving PSA-independent, study-mandated prostate biopsies.

Methods: We conducted a post-hoc analysis of data from 4,974 non-statin users in REDUCE, a randomized trial in men with elevated PSA and a negative baseline biopsy. Men underwent 2- and 4-year trial-mandated prostate biopsies. Associations between baseline serum levels of total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and prostate cancer risk, overall and by Gleason grade (<7 vs. ≥ 7), were examined using multivariable logistic regression.

Results: High total serum cholesterol was associated with an increased risk of high-grade prostate cancer diagnosis ($OR_{per10mg/dl}$ 1.05; 95% CI 1.00-1.09; $p=0.048$), but cholesterol was unrelated to either overall or low-grade prostate cancer risk (p -values >0.185). There was no association between serum LDL and overall, low- or high-grade prostate cancer risk (p -values >0.137). In contrast, elevated serum HDL was associated with increased risk of both overall ($OR_{per10mg/dl}$ 1.08; 95% CI 1.01-1.16; $p=0.033$) and high-grade prostate cancer ($OR_{per10mg/dl}$ 1.14; 95% CI 1.01-1.28; $p=0.034$).

Conclusions: In REDUCE, where all men received PSA-independent, trial-mandated biopsies thus ensuring complete prostate cancer ascertainment, high total serum cholesterol and high

HDL were associated with increased risk of high-grade prostate cancer, supporting a cholesterol-prostate cancer link.

Introduction

Obesity is associated with increased risk of several different cancer types, including aggressive prostate cancer.^{1,2} Hypercholesterolemia, an obesity-associated comorbidity,³ promotes tumor proliferation and inflammation. In addition, cholesterol is the precursor to androgens, essential for prostate cancer development and growth.⁴ Indeed, preclinical studies in mouse models of prostate cancer reported increased risk of tumor development and enhanced tumor growth in mice fed a cholesterol-enriched diet.⁵⁻⁷

In contrast, findings from epidemiologic studies examining the association between hypercholesterolemia and prostate cancer are conflicting. While some found high cholesterol to be associated with increased risk of both overall and high-grade prostate cancer,^{8,9} others reported inverse associations,¹⁰ and a recent meta-analysis reported no significant association between total cholesterol, high-density lipoprotein (HDL), or low-density lipoprotein (LDL) and risk of overall or high-grade prostate cancer.¹¹ Two potential sources of bias may have influenced prior study findings. Serum cholesterol is positively correlated with serum prostate-specific antigen (PSA),^{12,13} potentially leading to increased PSA-driven biopsy rates and more prostate cancer diagnoses among men with high cholesterol. Conversely, obesity-associated comorbidities including hypercholesterolemia have been associated with lower biopsy compliance,^{14,15} potentially leading to fewer prostate cancer diagnoses among men with high cholesterol.

To minimize the contribution of these potential biases, we tested the association between serum cholesterol and prostate cancer risk using data from REduction by DUtasteride of prostate Cancer Events (REDUCE), a randomized trial where all men received prostate biopsies regardless of PSA or other clinical factors. Given preclinical data linking cholesterol to the

development and progression of prostate cancer,⁵ we hypothesized that elevated serum cholesterol would be associated with increased risk of prostate cancer.

Patients and Methods

Study design

REDUCE, a prostate cancer chemoprevention trial, randomized men to dutasteride vs. placebo.¹⁶ Eligible men were 50-75 years old, with a PSA of 2.5-10.0 ng/ml if 50-60 years or 3.0-10.0 ng/ml if >60 years, and had a single, negative study-independent prostate biopsy (6-12 cores) within 6 months prior to enrollment. Ineligible men had a past history of prostate cancer, prostate surgery, prostate volume >80ml, or International Prostate Symptom Score >25 or >20 on alpha-blockers. Trial-mandated ten-core transrectal ultrasound (TRUS)-guided prostate biopsies were performed at 2- and 4-years post randomization regardless of PSA. Protocol-independent biopsies were performed at the physician's discretion. High density lipoprotein (HDL), low density lipoprotein (LDL), and total cholesterol were measured by Quest Diagnostic (Van Nuys, California, USA) at the baseline study visit, after enrollment but before randomization.

Participants

REDUCE enrolled 8,122 men in the efficacy population. We excluded men with missing baseline data on race (n=1), body mass index (BMI; n=131), PSA (n=18), digital rectal exam (DRE) findings (n=9), history of coronary artery disease (CAD; n=2), family history of prostate cancer (n=6), smoking status (n=3), diabetes (n=1), alcohol use (n=40), total cholesterol (n=151), and LDL (n=189). While baseline statin data were available, we were unable to control for duration of statin use before enrollment or for continued statin use during the trial; therefore, we excluded men using statins (n=1,335) and/or other lipid-lowering therapy (n=134) at baseline. Differences in baseline characteristics in REDUCE by statin use have been previously published.¹⁷ As baseline HDL and cholesterol did not follow parametric distributions, 129 men with HDL or cholesterol values $\geq$ three standard deviations outside the mean were excluded.

Finally, of the remaining 5,973 men, a further 999 were excluded who did not receive any on-study biopsies, leaving a study population of 4,974.

Statistical Analysis

We examined associations between each lipid type and risk of prostate cancer diagnosis, treating lipids as both continuous and categorical variables, with categories defined using National Cholesterol Education Program Adult Treatment Panel III guidelines.¹⁸ Our primary exposure was total serum cholesterol, with HDL and LDL treated as secondary exposure variables. As not all men in the efficacy population received both the 2- and 4-year trial-mandated biopsies, we explored the association between demographic and clinical characteristics and biopsy compliance. Total serum cholesterol level was not associated with biopsy compliance at the 2-year biopsy. As such, to ensure all men had equal opportunity for prostate cancer diagnosis regardless of cholesterol level, we considered the 2-year biopsy as our primary outcome, among men who received the 2-year biopsy.

Differences in baseline demographic and clinical characteristics across cholesterol categories were tested using ANOVA, Kruskal-Wallis and χ^2 for continuous parametric, continuous non-parametric and categorical variables respectively. We tested the relationship between continuous serum cholesterol, LDL and HDL levels using Pearson's correlation. Logistic regression was used to examine associations between lipids and prostate cancer risk, adjusting for baseline age (continuous), race (white, non-white), BMI (continuous), PSA (continuous), DRE findings (normal, abnormal), CAD history (yes, no), family history of prostate cancer (yes, no), smoking status (current, former, never), diabetes (yes, no), alcohol use (none, ≤ 7 units/week, > 7 units/week), region (North America, Europe, other), and treatment arm (placebo, dutasteride). Given weak correlations between total cholesterol, LDL and HDL

(Supplementary Table 1), we mutually adjusted analyses for other lipid types. Continuous lipid levels were presented in 10 mg/dL increments to aid interpretation of odds ratios.

We used multinomial logistic regression to examine the relationship between lipids and prostate cancer risk by disease grade, adjusting for aforementioned covariates. High-grade prostate cancer was defined as Gleason score ≥ 7 , and low-grade prostate cancer as Gleason score < 7 , as previously published in REDUCE.¹⁷ Given the potential interaction between treatment arm and lipids in predicting risk of prostate cancer diagnosis, we tested whether randomization to placebo vs. dutasteride was a significant effect modifier of the association between lipids and prostate cancer risk by incorporating a cross product term along with the primary variables in the multivariable analysis.

Statistical significance was defined as $p < 0.05$. All analysis was performed using Stata v13.1 (StataCorp, College Station, TX USA).

Results

Patient demographics

Average baseline serum cholesterol level was 222.5 mg/dL. Men with higher cholesterol were older ($p=0.002$), more likely to be white ($p=0.001$) and European ($p<0.001$), had a higher BMI ($p<0.001$), and were more likely to have diabetes ($p<0.001$). Men with high cholesterol had lower alcohol intake ($p=0.010$) and were less likely to have a family history of prostate cancer ($p=0.004$). No significant associations were seen between serum cholesterol and baseline PSA, history of CAD, smoking status or treatment arm (Table 1).

Biopsy compliance

Non-white race ($p=0.035$), North American location ($p=0.001$), low baseline LDL ($p=0.043$) and randomization to the placebo arm ($p=0.042$) were associated with lower likelihood of receiving at least one on-study biopsy. Baseline HDL, cholesterol, BMI, PSA, history of CAD, baseline DRE findings, and baseline age were unrelated to biopsy compliance (data not shown). However, among men with a negative 2-year biopsy, those with high cholesterol were less likely to receive the 4-year biopsy ($p=0.023$). Given this, we selected prostate cancer risk at the 2-year biopsy as our primary endpoint, as cholesterol was not significantly associated with compliance at the study-mandated 2-year biopsy ($p=0.408$). Risk of prostate cancer diagnosis at any time during the study period was examined as a secondary outcome.

Interaction between lipids and treatment arm in predicting prostate cancer risk

We found similar associations between total cholesterol and overall prostate cancer risk in both arms (p -interaction= 0.091). Similarly, there was no significant interaction between total serum cholesterol and treatment arm for the outcomes of low- or high-grade prostate cancer (all

p-interactions ≥ 0.103), and no interactions between HDL or LDL and treatment arm for overall, low-, or high-grade prostate cancer (all p-interactions ≥ 0.433). As such, both arms were combined for all analyses.

Relationship between total serum cholesterol and prostate cancer risk

There were no significant associations between total serum cholesterol categories and risk of overall, low- or high-grade prostate cancer at the 2-year biopsy on univariable or multivariable analysis (all p-values ≥ 0.185 ; Table 2). However, there was a significant positive relationship between continuous cholesterol levels and risk of high-grade prostate cancer at the 2-year biopsy in univariable (OR_{per 10mg/dL} 1.05; 95% CI 1.01-1.09; p=0.019) and multivariable analysis (OR_{per 10mg/dL} 1.05; 95% CI 1.00-1.09; p=0.048). No significant association was seen between continuous cholesterol level and risk of overall or low-grade prostate cancer.

Further analysis was performed to examine the relationship between serum cholesterol and risk of prostate cancer diagnosis at any biopsy during the study period, recognizing that patients with elevated cholesterol were less likely to receive the study-mandated 4-year biopsy (thus reducing the opportunity to have prostate cancer diagnosed). In this setting, no significant association was seen between cholesterol and prostate cancer risk on either univariable or multivariable analysis, regardless of whether cholesterol was modeled as a continuous or categorical variable (all p-values ≥ 0.401 ; Supplementary Table 2). Furthermore, when stratified by disease grade, no significant relationship between cholesterol and low- or high-grade prostate cancer risk was seen (all p-values ≥ 0.097).

Relationship between serum HDL and LDL and prostate cancer risk

Serum LDL was not associated with overall prostate cancer risk at the 2-year biopsy on univariable or multivariable analysis (all p-values ≥ 0.218 ; Table 3). When stratified by disease

grade, no significant associations were seen between categorical or continuously-coded LDL and low- or high-grade prostate cancer risk (all p-values ≥ 0.137 ; Table 3). When examining the association between LDL and risk of prostate cancer diagnosis at any time during the study period, similar null findings were seen (Supplementary Table 3).

In contrast to relatively null findings for LDL, HDL was positively associated with a higher risk of overall prostate cancer on both univariable ($p < 0.004$) and multivariable analysis ($OR_{\text{per } 10\text{mg/dL}} 1.08$; 95% CI 1.01-1.16; $p = 0.033$). When stratified by disease grade, on multivariable analysis, each 10 mg/dL increase in HDL was associated with an increased risk of high-grade prostate cancer ($OR_{\text{per } 10\text{mg/dL}} 1.14$; 95% CI 1.01-1.28; $p = 0.034$). HDL was associated with an increased risk of low-grade prostate cancer in univariable analysis ($OR_{\text{per } 10\text{mg/dL}} 1.08$; 95% CI 1.00-1.17; $p = 0.040$), but this association was not significant on multivariable analysis ($OR_{\text{per } 10\text{mg/dL}} 1.06$; 95% CI 0.97-1.14; $p = 0.197$). Similar patterns of association were seen between HDL and prostate cancer diagnosed at any point during the study period (Supplementary Table 3).

Discussion

Cholesterol as a risk factor for prostate cancer remains controversial. Despite pre-clinical data showing a role for serum cholesterol in prostate cancer growth, results from epidemiologic studies are mixed. We tested the association between serum cholesterol and risk of prostate cancer diagnosis in REDUCE, where men with a negative baseline prostate biopsy underwent trial-mandated, PSA-independent biopsies at 2- and 4-years. Our findings demonstrate an association between high serum cholesterol and HDL and increased risk of high-grade prostate cancer in a setting where trial-mandated biopsies ensured complete cancer ascertainment. These data support a role for cholesterol, a modifiable risk factor, in aggressive prostate cancer.

Prostate cancer is unique in its dependence on androgens for growth.¹⁹ Cholesterol is the precursor for androgen synthesis by the prostate, leading to the hypothesis that increased serum cholesterol levels may be associated with a higher prostate cancer risk. Zhuang *et al* showed that a cholesterol-enriched diet promoted tumor growth in a xenograft mouse model of prostate cancer, compared to control diet.⁵ Another study showed that lowering serum cholesterol in xenograft mouse model of prostate cancer reduced tumor androgen concentrations and slowed tumor growth.²⁰ In contrast to these pre-clinical data supporting a cholesterol-prostate cancer link, findings from epidemiologic studies remain mixed. Analysis of the placebo arm of the Prostate Cancer Prevention Trial (PCPT) showed reduced risk of high-grade prostate cancer in men with lower cholesterol levels,⁹ and a study from the Veterans Administration found that high serum cholesterol was associated with increased high-grade prostate cancer risk.²¹ An association between high serum cholesterol and increased prostate cancer risk is also supported by results from the Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) cohort.⁸ However, a meta-analysis of these and other studies reported no significant association

between serum cholesterol and risk of either overall or high-grade prostate cancer.²² Given that past studies were conducted during the PSA-screening era, it is possible that their results were affected by the positive correlation between cholesterol and PSA.^{12,13} Factors influencing PSA levels may affect PSA-driven recommendations for prostate biopsy thereby influencing biopsy rates. Moreover, observational studies are rarely able to control for biopsy compliance, which differs by obesity and obesity-associated co-morbidity status.^{14,15} Data from the PCPT chemoprevention trial that, like REDUCE, implemented trial-mandated PSA-independent biopsies, showed that men with low serum cholesterol had lower high-grade prostate cancer risk. As such, our study builds on evidence for a cholesterol-prostate cancer link in the context of PSA-independent, trial-mandated biopsies where all men had equal opportunity for prostate cancer diagnosis.

Relatively few studies have examined the association between HDL and prostate cancer risk, reporting mixed findings. A Swedish cohort including ~1,500 prostate cancer cases found that high HDL was inversely associated with overall prostate cancer risk.²³ An analysis of the Finnish ATBC cohort also reported an inverse association between HDL level and risk of prostate cancer,⁸ while a study of the US Veterans Administration reported that high HDL was associated with increased risk of overall and high-grade prostate cancer.²¹ However, a meta-analysis of these and a number of other null studies reported no significant association between serum HDL and prostate cancer risk.²² Given anti-inflammatory, anti-proliferative and anti-oxidant properties of HDL,²⁴ it is unclear why high HDL would be associated with an increased, and not decreased, risk of prostate cancer, as we found in the present study. However, as some data are now challenging the long-hypothesized cardio-protective role of HDL,²⁵ alongside a meta-analysis showing that drugs increasing HDL do not reduce cardiovascular risk further

questioning the health “benefits” of higher HDL,²⁶ further study is needed to define the link between high HDL and increased risk of prostate cancer.

Our findings should be considered in the context of the strengths and weaknesses of this study. First, eligibility criteria for REDUCE ensured that all men had baseline PSA levels between 2.5 and 10 ng/ml. In addition, various exclusion criteria in REDUCE increased the homogeneity of the sample, but may limit the generalizability of our results. Second, serum cholesterol levels were assessed at a single time point and therefore do not capture any potential variability in cholesterol levels over time. However, the optimal timing or “window of susceptibility” for prostate cancer development to be influenced by serum cholesterol is not known. Moreover, any exposure misclassification would likely be non-differential between groups and therefore bias our results towards the null. Third, we found that high total serum cholesterol and HDL, both coded as continuous variables, were associated with increased risk of high-grade prostate cancer, while National Cholesterol Education Program-defined categories of cholesterol and HDL were not significantly associated with high-grade prostate cancer risk. However, the thresholds at which serum cholesterol could influence prostate cancer risk may be different than those established for cardiovascular disease risk and therefore continuous levels may provide a more appropriate measure of exposure in the context of prostate cancer risk. Fourth, although we excluded men using statins at baseline, some men may have initiated statin use during the trial period. However, for these men, our lipid measures were taken prior to statin use. Moreover, any statin-mediated changes in lipids during the trial period would likely bias our results towards the null given the inverse association between statins and aggressive prostate cancer risk²⁷. Finally, although we were able to adjust our models for a number of potential

confounders, we lacked data on diet and physical activity. Study strengths include the large, multinational population in REDUCE, and PSA-independent on-study biopsies.

In conclusion, using data from the REDUCE trial, where men underwent PSA-independent prostate biopsies, we found that high total serum cholesterol and high HDL were associated with increased risk of high-grade prostate cancer. Together with findings from PCPT, another trial which implemented mandatory PSA-independent biopsies, our results support an association between serum cholesterol and increased risk of high-grade prostate cancer where PSA-independent, trial-mandated biopsies ensured that all men had equal opportunity for prostate cancer detection. These findings, combined with evidence that use of the cholesterol-lowering statins is associated with reduced risk of high-grade prostate cancer, suggest that serum lipid levels should be explored as modifiable risk factors for aggressive prostate cancer.

Conflict of interest: The REDUCE study was funded by GlaxoSmithKline. Dr Castro-Santamaria is an employee of GlaxoSmithKline. Dr Andriole is a consultant for GlaxoSmithKline. None of the other authors declare any conflicts of interest.

References

1. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nat Rev Cancer* 2004; **4**(8): 579-591.
2. Allott EH, Masko EM, Freedland SJ. Obesity and prostate cancer: weighing the evidence. *European urology* 2013; **63**(5): 800-809.
3. Ishikawa-Takata K, Ohta T, Moritaki K, Gotou T, Inoue S. Obesity, weight change and risks for hypertension, diabetes and hypercholesterolemia in Japanese men. *Eur J Clin Nutr* 2002; **56**(7): 601-607.
4. Pelton K, Freeman MR, Solomon KR. Cholesterol and prostate cancer. *Curr Opin Pharmacol* 2012; **12**(6): 751-759.
5. Zhuang L, Kim J, Adam RM, Solomon KR, Freeman MR. Cholesterol targeting alters lipid raft composition and cell survival in prostate cancer cells and xenografts. *J Clin Invest* 2005; **115**(4): 959-968.
6. Llaverias G, Danilo C, Wang Y, Witkiewicz AK, Daumer K, Lisanti MP *et al.* A Western-type diet accelerates tumor progression in an autochthonous mouse model of prostate cancer. *Am J Pathol* 2010; **177**(6): 3180-3191.
7. Solomon KR, Pelton K, Boucher K, Joo J, Tully C, Zurakowski D *et al.* Ezetimibe is an inhibitor of tumor angiogenesis. *Am J Pathol* 2009; **174**(3): 1017-1026.
8. Mondul AM, Weinstein SJ, Virtamo J, Albanes D. Serum total and HDL cholesterol and risk of prostate cancer. *Cancer causes & control : CCC* 2011; **22**(11): 1545-1552.
9. Platz EA, Till C, Goodman PJ, Parnes HL, Figg WD, Albanes D *et al.* Men with low serum cholesterol have a lower risk of high-grade prostate cancer in the placebo arm of the prostate cancer prevention trial. *Cancer Epidemiol Biomarkers Prev* 2009; **18**(11): 2807-2813.
10. Heir T, Falk RS, Robsahm TE, Sandvik L, Erikssen J, Tretli S. Cholesterol and prostate cancer risk: a long-term prospective cohort study. *BMC cancer* 2016; **16**: 643.
11. YuPeng L, YuXue Z, PengFei L, Cheng C, YaShuang Z, DaPeng L *et al.* Cholesterol Levels in Blood and the Risk of Prostate Cancer: A Meta-analysis of 14 Prospective Studies. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 2015; **24**(7): 1086-1093.
12. Zapata D, Howard LE, Allott EH, Hamilton RJ, Goldberg K, Freedland SJ. Is PSA related to serum cholesterol and does the relationship differ between black and white men? *The Prostate* 2015; **75**(16): 1877-1885.

13. Hamilton RJ, Goldberg KC, Platz EA, Freedland SJ. The influence of statin medications on prostate-specific antigen levels. *Journal of the National Cancer Institute* 2008; **100**(21): 1511-1518.
14. Fischer S, Sun S, Howard LE, Moreira DM, Castro-Santamaria R, Andriole GL *et al.* Baseline subject characteristics predictive of compliance with study-mandated prostate biopsy in men at risk of prostate cancer: results from REDUCE. *Prostate cancer and prostatic diseases* 2016; **19**(2): 202-208.
15. Tangen CM, Goodman PJ, Till C, Schenk JM, Lucia MS, Thompson IM, Jr. Biases in Recommendations for and Acceptance of Prostate Biopsy Significantly Affect Assessment of Prostate Cancer Risk Factors: Results From Two Large Randomized Clinical Trials. *J Clin Oncol* 2016; **34**(36): 4338-4344.
16. Andriole G, Bostwick D, Brawley O, Gomella L, Marberger M, Tindall D *et al.* Chemoprevention of prostate cancer in men at high risk: rationale and design of the reduction by dutasteride of prostate cancer events (REDUCE) trial. *The Journal of urology* 2004; **172**(4 Pt 1): 1314-1317.
17. Freedland SJ, Hamilton RJ, Gerber L, Banez LL, Moreira DM, Andriole GL *et al.* Statin use and risk of prostate cancer and high-grade prostate cancer: results from the REDUCE study. *Prostate cancer and prostatic diseases* 2013; **16**(3): 254-259.
18. National Cholesterol Education Program Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002; **106**(25): 3143-3421.
19. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L *et al.* Abiraterone and increased survival in metastatic prostate cancer. *The New England journal of medicine* 2011; **364**(21): 1995-2005.
20. Mostaghel EA, Solomon KR, Pelton K, Freeman MR, Montgomery RB. Impact of circulating cholesterol levels on growth and intratumoral androgen concentration of prostate tumors. *PloS one* 2012; **7**(1): e30062.
21. Farwell WR, D'Avolio LW, Scranton RE, Lawler EV, Gaziano JM. Statins and prostate cancer diagnosis and grade in a veterans population. *Journal of the National Cancer Institute* 2011; **103**(11): 885-892.
22. YuPeng L, YuXue Z, PengFei L, Cheng C, YaShuang Z, DaPeng L *et al.* Cholesterol Levels in Blood and the Risk of Prostate Cancer: A Meta-analysis of 14 Prospective Studies. *Cancer Epidemiol Biomarkers Prev* 2015.

23. Van Hemelrijck M, Walldius G, Jungner I, Hammar N, Garmo H, Binda E *et al.* Low levels of apolipoprotein A-I and HDL are associated with risk of prostate cancer in the Swedish AMORIS study. *Cancer causes & control : CCC* 2011; **22**(7): 1011-1019.
24. Toth PP. High-density lipoprotein as a therapeutic target: clinical evidence and treatment strategies. *Am J Cardiol* 2005; **96**(9A): 50K-58K; discussion 34K-35K.
25. Voight BF, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, Jensen MK *et al.* Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. *Lancet* 2012; **380**(9841): 572-580.
26. Keene D, Price C, Shun-Shin MJ, Francis DP. Effect on cardiovascular risk of high density lipoprotein targeted drug treatments niacin, fibrates, and CETP inhibitors: meta-analysis of randomised controlled trials including 117,411 patients. *BMJ* 2014; **349**: g4379.
27. Tan P, Wei S, Tang Z, Gao L, Zhang C, Nie P *et al.* LDL-lowering therapy and the risk of prostate cancer: a meta-analysis of 6 randomized controlled trials and 36 observational studies. *Sci Rep* 2016; **6**: 24521.

Table 1: Baseline characteristics of the REDUCE study population according to total serum cholesterol levels.

	Total serum cholesterol level			p-value*
	Normal (<200 mg/dL)	Borderline (200-239 mg/dL)	High (≥240 mg/dL)	
Total patients, n (%)	1,037 (20.9)	2,948 (59.3)	989 (19.9)	
Age, mean (SD)	62.3 (6.2)	62.4 (5.9)	63.4 (5.9)	0.002†
Race, n (%)				0.001
White	918 (88.5)	2,718 (92.2)	913 (92.3)	
Non-white	119 (11.5)	230 (7.8)	76 (7.7)	
Region (%)				<0.001
North America	272 (26.2)	575 (19.5)	127 (12.8)	
Europe	576 (55.5)	1,903 (64.6)	739 (74.7)	
Other	189 (18.2)	470 (15.9)	123 (12.4)	
Body mass index (kg/m²), median (IQR)	26.0 (24.0-28.4)	26.7 (24.7-29.0)	27.4 (25.2-29.9)	<0.001†
PSA (ng/ml), median (IQR)	5.7 (4.4-7.4)	5.8 (4.4-7.4)	5.7 (4.4-7.4)	0.922††
Abnormal DRE, n (%)	49 (4.7)	88 (3.0)	28 (2.8)	0.017
History of CAD, n (%)	44 (4.2)	157 (5.3)	51 (5.2)	0.389
Family history of prostate cancer, n (%)	153 (14.8)	369 (12.5)	98 (9.9)	0.004
Smoking history, n (%)				0.071
Never	498 (48.0)	1,398 (47.4)	452 (45.7)	
Former	361 (34.8)	1,130 (38.3)	392 (39.6)	
Current	178 (17.2)	420 (14.3)	145 (14.7)	
Diabetes, n (%)				<0.001
No	1,005 (97)	2,876 (98)	824 (83)	
Yes	32 (3)	72 (2)	165 (17)	
Alcohol intake, n (%)				0.010
None	297 (29)	682 (23)	231 (23)	
≤7 units per week	488 (47)	1,486 (50)	497 (50)	
>7 units per week	252 (24)	780 (26)	261 (16)	
Treatment (%)				0.698
Placebo	541 (52.2)	1,496 (50.8)	511 (51.7)	
Dutasteride	496 (47.8)	1,452 (49.3)	478 (48.3)	

Abbreviations: PSA (prostate specific antigen), SD (standard deviation), IQR (interquartile range, Q1-Q3), DRE (digital rectal exam), CAD (coronary artery disease)

*P value by χ^2 , except where noted; †P value by ANOVA; †† P value by Kruskal-Wallis

Table 2: Associations between total serum cholesterol levels and prostate cancer risk at the 2-year biopsy in REDUCE

	Overall prostate cancer		Low-grade prostate cancer		High-grade prostate cancer	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Total cholesterol						
<i>Unadjusted</i>						
Normal	1.00 (Ref)	-	1.00 (Ref)	-	1.00 (Ref)	-
Borderline	0.87 (0.71-1.07)	0.185	0.88 (0.70-1.11)	0.289	0.85 (0.59-1.22)	0.373
High	0.96 (0.75-1.23)	0.741	0.84 (0.63-1.13)	0.261	1.24 (0.82-1.88)	0.297
<i>Per 10 mg/dl</i>	<i>1.01 (0.99-1.04)</i>	<i>0.255</i>	<i>1.00 (0.97-1.03)</i>	<i>0.920</i>	<i>1.05 (1.01-1.09)</i>	<i>0.019</i>
<i>Adjusted*</i>						
Normal	1.00 (Ref)	-	1.00 (Ref)	-	1.00 (Ref)	-
Borderline	0.88 (0.72-1.09)	0.243	0.89 (0.70-1.13)	0.334	0.87 (0.60-1.26)	0.465
High	0.94 (0.72-1.23)	0.656	0.83 (0.61-1.14)	0.246	1.23 (0.79-1.90)	0.366
<i>Per 10 mg/dl</i>	<i>1.01 (0.99-1.04)</i>	<i>0.347</i>	<i>1.00 (0.97-1.03)</i>	<i>0.895</i>	<i>1.05 (1.00-1.09)</i>	<i>0.048</i>

*adjusted for age, race, geographic region, PSA, BMI, baseline DRE, family history of prostate cancer, coronary artery disease, smoking status, diabetes, alcohol use, treatment group, LDL level and HDL level

Table 3: Association between serum levels of LDL and HDL and prostate cancer risk at the 2-year biopsy in REDUCE

	Overall prostate cancer risk		Low-grade prostate cancer		High-grade prostate cancer	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
LDL[†]						
<i>Unadjusted</i>						
Normal	1.00 (Ref)	-	1.00 (Ref)	-	1.00 (Ref)	-
Borderline	1.05 (0.80-1.37)	0.723	1.23 (0.88-1.71)	0.229	0.77 (0.51-1.18)	0.233
High	0.92 (0.68-1.24)	0.567	1.05 (0.73-1.51)	0.809	0.71 (0.44-1.15)	0.165
<i>Per 10 mg/dl</i>	<i>0.99 (0.97-1.02)</i>	<i>0.451</i>	<i>1.00 (0.97-1.02)</i>	<i>0.749</i>	<i>0.98 (0.94-1.02)</i>	<i>0.345</i>
<i>Adjusted*</i>						
Normal	1.00 (Ref)	-	1.00 (Ref)	-	1.00 (Ref)	-
Borderline	1.04 (0.79-1.37)	0.769	1.19 (0.85-1.66)	0.311	0.80 (0.52-1.24)	0.326
High	0.86 (0.63-1.18)	0.347	0.97 (0.67-1.42)	0.886	0.68 (0.42-1.13)	0.137
<i>Per 10 mg/dl</i>	<i>0.98 (0.96-1.01)</i>	<i>0.218</i>	<i>0.99 (0.96-1.02)</i>	<i>0.433</i>	<i>0.98 (0.93-1.02)</i>	<i>0.260</i>
HDL^{††}						
<i>Unadjusted</i>						
Low	1.00 (Ref)	-	1.00 (Ref)	-	1.00 (Ref)	-
Borderline	1.20 (0.96-1.50)	0.106	1.17 (0.90-1.51)	0.235	1.28 (0.86-1.90)	0.219
Normal	1.30 (0.99-1.69)	0.055	1.24 (0.91-1.70)	0.167	1.43 (0.90-2.28)	0.130
<i>Per 10 mg/dl</i>	<i>1.10 (1.03-1.17)</i>	<i>0.004</i>	<i>1.08 (1.00-1.17)</i>	<i>0.040</i>	<i>1.14 (1.02-1.27)</i>	<i>0.017</i>
<i>Adjusted*</i>						
Low	1.00 (Ref)	-	1.00 (Ref)	-	1.00 (Ref)	-
Borderline	1.17 (0.93-1.47)	0.176	1.12 (0.86-1.46)	0.397	1.31 (0.87-1.97)	0.197
Normal	1.19 (0.90-1.58)	0.215	1.12 (0.81-1.55)	0.490	1.39 (0.85-2.28)	0.190
<i>Per 10 mg/dl</i>	<i>1.08 (1.01-1.16)</i>	<i>0.033</i>	<i>1.06 (0.97-1.14)</i>	<i>0.197</i>	<i>1.14 (1.01-1.28)</i>	<i>0.034</i>

*adjusted for age, race, geographic region, PSA, BMI, DRE, family history of prostate cancer, coronary artery disease, smoking status, diabetes, alcohol use, treatment group, total cholesterol level

[†]LDL analysis additionally adjusted for HDL level

^{††}HDL analysis additionally adjusted for LDL level